nicotine pharmacology. The studies conducted by Philip Morris ranged from traditional pharmacology involving animal experiments to EEG experiments.

Philip Morris conducted a large number of studies. In 1979 alone at least 16 different studies on nicotine pharmacology were conducted by three different research groups within Philip Morris' Behavioral Research Laboratory.[425] The Animal Behavior Group conducted six experiments on the drug effects of nicotine in rats. The Neuropsychology Laboratory conducted five experiments to determine the pharmacological effects of nicotine on the human brain, including experiments on "[t]he Effects of Cigarette Smoking on the Electroencephalogram" and "[L]ong-Term Smoke Deprivation and the Electrical Activity of the Brain."[426] The Smoking Behavior Group conducted studies on the behavioral consequences of smoking, including studies to determine the consequences of smoking low-nicotine cigarettes.

Beginning before 1980 and continuing until 1984, Philip Morris conducted research in search of a "nicotine analogue." This research demonstrates Philip Morris' knowledge that nicotine has the hallmark properties of a drug of abuse and shows the company's intention to preserve these properties in new products. As described by former Philip Morris scientist Victor DeNoble, the purpose of the research was "to come up with a molecule that would *mimic nicotine's effect in the brain*, and would not affect the peripheral nervous system and therefore not have cardiovascular liability."[427] Thus, while

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[425] Dunn WL (Philip Morris Inc.), *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7668-7670 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[426] *Id.* at H7669-7670.

[427] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 33 (Apr. 28, 1994) (testimony of Victor DeNoble) (emphasis added). *See* AR (Vol. 708 Ref. 2).

the company attempted to eliminate an adverse effect of nicotine, it deliberately sought to retain nicotine's effects on the brain.

To conduct this work, Philip Morris scientists had to identify and compare the pharmacological and behavioral effects of nicotine on the brain. The pharmacological and behavioral profiles of the nicotine analogues synthesized by Philip Morris chemists were then compared to those of nicotine.[428] Since the primary goal of the nicotine analogue program was to develop a nicotine analogue that would retain the physiological and behavioral effects of nicotine on the brain, especially its reinforcing properties, the newly synthesized nicotine analogues were screened in animal behavioral tests designed to assess their reinforcing properties. (A substance has reinforcing properties if it is able to induce repeated, compulsive use. *See* section II.A.3.c.i., above.) The tests used were "exactly the same tests" that the National Institute on Drug Abuse (NIDA) uses "to determine if a drug has an abuse potential."[429]

One of the principal NIDA tests used by Philip Morris was a series of "self-administration" experiments with rats. These studies determine addiction potential by assessing whether rats will press a lever to give themselves repeated injections of the test substance. There is a strong correlation between substances that are found to be self-

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[428] *Id.* at 5.

See also Declaration of Victor DeNoble of Feb. 2, 1995, at 2-9. *See* AR (Vol. 31 Ref. 524-5).

[429] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong,, 2d Sess. 17 (Apr. 28, 1994) (testimony of Victor DeNoble). *See* AR (Vol. 708 Ref. 2).

administered in rats and substances that are addictive in humans.[430] Philip Morris found that rats would self-administer nicotine.[431] According to the director of NIDA, "[t]hese findings from the DeNoble study indicate that nicotine has reinforcing properties, *one of the hallmark characteristics of an addictive drug*."[432] The Philip Morris researchers also found that rats would develop a tolerance to nicotine, another characteristic of an addictive drug.[433]

The senior management and top officials of Philip Morris "continually reviewed . . . and approved" this research.[434] In fact, in November 1983, the president of Philip Morris, Shep Pollack, visited the laboratory conducting the self-administration experiments and watched rats inject themselves with nicotine. Pollack was informed by the Philip Morris researcher in charge of the study, Victor DeNoble, that Philip Morris' self-administration studies followed "the exact procedure that NIDA would use to demonstrate abuse liability," and that the studies demonstrated that nicotine is "a reinforcing agent."[435] DeNoble further informed Pollack that although a finding of self-

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[430] Gardner EL, Brain reward mechanism, in *Substance Abuse, A Comprehensive Textbook*, 2d ed., eds. Lowinson JH, Ruiz P, Millman RB, *et al.* (Baltimore: Williams and Wilkins 1992), at 70. *See* AR (Vol. 8 Ref. 88).

See also section II.A.3.c.i.

[431] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 5 (Apr. 28, 1994) (testimony of Victor DeNoble). *See* AR (Vol. 708 Ref. 2).

[432] *Id.* at 20 (letter from Leshner AI (NIDA) to Waxman HA (Apr. 13, 1994) (emphasis added)).

[433] *Id.* at 5 (testimony of Victor DeNoble). The Philip Morris researchers did not, however, find evidence of nicotine withdrawal.

[434] *Id.* at 5-6.

[435] *Id.* at 54.

administration does not by itself prove that nicotine is addictive, it "predicts abuse liability."[436] Despite several attempts, DeNoble and his colleague Paul Mele were not allowed to publish the results of their self-administration studies or present their results at a meeting sponsored by the American Psychological Association.[437]

These studies were conducted for their potential commercial applicability. The memorandum describing the "plans and objectives" for the Behavioral Research Laboratory in 1979 states expressly that "the rationale for the program rests on the premise that such knowledge will strengthen Philip Morris R&D capability in developing new and improved smoking products."[438]

Some of Philip Morris' research attempted to assess the pharmacological effects of nicotine on youths. One study on the hyperkinetic child as prospective smoker observed that "amphetamines, which are strong stimulants, have the anomalous effect of quieting these children down"; the Philip Morris researchers initiated a study to determine "whether such children may not eventually become cigarette smokers in their teenage years as they discover *the advantage of self-stimulation via nicotine*."[439] This study was apparently

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[436] *Id.*

[437] *Id.* at 51-52, 57-94.

[438] Dunn WL, *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7669. *See* AR (Vol. 14 Ref. 175a).

[439] Ryan FJ (Philip Morris Inc.), Relationship between smoking and personality, in *Smoker Psychology/May 1-31, 1974* (Jun. 10, 1974), in 141 Cong. Rec. H7651 (daily ed. Jul. 25, 1995) (emphasis added). *See* AR (Vol. 14 Ref. 175a).

For a further description of Philip Morris' research into hyperkinetic children, s*ee* the following documents reprinted in 141 Cong. Rec. H7651-7657 (daily ed. Jul. 25, 1995):

> Ryan FJ (Philip Morris Inc.), Relationship between smoking and personality, in *Smoker Psychology/May 1-31, 1974* (Jun. 10, 1974). *See* AR (Vol. 14 Ref. 175a).

never completed because "[o]bstacles presented by school systems and physicians . . . have made it very difficult for us to conduct studies using school and medical records of minors."[440] Another study initiated by Philip Morris involved administering "painful" electric shocks to college students to determine the anxiety-reducing effects of cigarettes.[441] Although preliminary findings supported the hypothesis that students with a high anxiety factor on personality tests would puff more frequently,[442] the study apparently had to be discontinued because "fear of shock is scaring away some of our more valuable

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Ryan FJ (Philip Morris Inc.), Hyperkinesis as a precursor of smoking, in *Smoker Psychology/Feb. 1-28, 1975* (Mar. 10, 1975). *See* AR (Vol. 14 Ref. 175a).

Philip Morris Research Center, *Behavioral Research Annual Report* (Jul. 18, 1975) (approved by Dunn WL). *See* AR (Vol. 14 Ref. 175a).

Ryan FJ (Philip Morris Inc.), Hyperactivity, in *Smoker Psychology/Apr. 1-30, 1977* (May 13, 1977). *See* AR (Vol. 14 Ref. 175a).

Ryan FJ (Philip Morris Inc.), Hyperkinetic children, in *Smoker Psychology/Feb. 1-28, 1978* (Mar. 10, 1978). *See* AR (Vol. 14 Ref. 175a).

[440] Ryan FJ (Philip Morris Inc.), Hyperkinetic children, in *Smoker Psychology/Feb. 1-28, 1978* (Mar. 10, 1978), in 141 Cong. Rec. H7657 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[441] Ryan FJ (Philip Morris Inc.), *Proposed Research Project: Smoking and Anxiety* (Dec. 23, 1969), in 141 Cong. Rec. H7648 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

For a further description of Philip Morris' research involving the administration of electric shocks, *see* the following documents printed in 141 Cong. Rec. H7648-7649 (daily ed. Jul. 25, 1995):

Ryan FJ (Philip Morris Inc.), Shock I, II, III, and IV, in *Consumer Psychology* (Sep. 16 - Oct.15, 1971). *See* AR (Vol. 14 Ref. 175a).

Ryan FJ (Philip Morris Inc.), Shock V, in *Consumer Psychology* (Jan. 15 - Feb. 15, 1972). *See* AR (Vol. 14 Ref. 175a).

Dunn WL (Philip Morris Inc.), *Quarterly Report-Projects 1600 and 2302* (Oct. 5, 1972). *See* AR (Vol. 14 Ref. 175a).

[442] Ryan FJ (Philip Morris Inc.), Shock I, II, III, and IV, in *Consumer Psychology Monthly Report* (Sep. 16 - Oct. 15, 1971), in 141 Cong. Rec. H7648-7649 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

subjects."[443] In another study, Philip Morris proposed injecting nicotine into human subjects in order "to yield a broader picture of the role of the spike, the level, and the reinforcement characteristics of the substance."[444]

In congressional testimony, the former Philip Morris president, William Campbell, testified that to the extent that Philip Morris controls nicotine levels in cigarettes through blending, this is done "for taste."[445] Philip Morris's research program does not support this statement, however. The internal research documents in the administrative record show that Philip Morris exhaustively investigated the pharmacological properties of nicotine—not its gustatory properties. The intensive focus on nicotine pharmacology reflected in the documents indicates that Philip Morris regarded nicotine's contribution to cigarettes as pharmacological, not taste-related. Moreover, in its comments Philip Morris did not provide evidence of internal Philip Morris research into the taste characteristics of nicotine.

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[443] Eichorn PA, Dunn WL (Philip Morris Inc.), *Quarterly Reports–Projects 1600 and 2302* (Oct. 5, 1972), in 141 Cong. Rec. H7649 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[444] Dunn WL (Philip Morris Inc.), *Plans and Objectives–1981* (Nov. 26, 1980), in 141 Cong. Rec. H7682 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

For a further description of Philip Morris' proposed research involving nicotine injections, *see*:

> Dunn WL (Philip Morris Inc.), *Behavioral Research Accomplishments, 1977* (Dec. 19, 1977), in 141 Cong. Rec. H7666 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).
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> Dunn WL (Philip Morris Inc.), *Plans and Objectives–1979* (Dec. 6, 1978), in 141 Cong. Rec. H7669 (daily ed. Jul. 25, 1995). *See* AR (Vol. 14 Ref. 175a).

[445] *Regulation of Tobacco Products (Part 1): Hearings Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 764 (Apr. 14, 1994) (testimony of William Campbell). *See* AR (Vol. 707 Ref. 1).

Further examples of Philip Morris' research on nicotine pharmacology are presented in the Jurisdictional Analysis. *See* 60 FR 41590–41591, 41595–41599. Taken together, these studies show that Philip Morris conducted an extensive, sustained, and sophisticated investigation into the pharmacological effects of nicotine that gave the company knowledge that nicotine has significant pharmacological effects on smokers, including reinforcing effects. The research was conducted because of its commercial significance to Philip Morris; used techniques that are employed by government agencies to identify the "abuse potential" of drugs; and found that nicotine has hallmark characteristics of an addictive drug, including reinforcing effects and the development of tolerance.

iii. Project Table. Philip Morris' recognition of the important pharmacological role of nicotine in cigarettes has been consistent for over three decades. New evidence received by the Agency during the comment period, for instance, indicates that officials inside Philip Morris continued to recognize the importance of nicotine's pharmacological effects and uses in the 1990's.

A draft Philip Morris report on "Project Table," a proposal to develop "a nicotine delivery device" that relies on "heating rather than burning the tobacco" to "produce[] a cleaner, safer smoking experience," written around 1992, acknowledges that although "[d]ifferent people smoke for different reasons. . . . *the primary reason is to deliver nicotine into their bodies.*"[446] The report describes nicotine in cigarettes in explicit drug-like terms:

[446] Philip Morris, Inc., Draft Report Regarding a Proposal for a "Safer" Cigarette, Code-named *Table*, at 1,5 (emphasis added). *See* AR (Vol. 531 Ref. 122).

> Nicotine . . . is a physiologically active, nitrogen containing substance. *Similar organic chemicals include . . . quinine, cocaine, atropine and morphine*. While each of these substances can be used to affect human physiology, nicotine has a particularly broad range of influence.[447]

Project Table provides a detailed description of the pharmacological action of nicotine on the brain:

> *During the smoking act, nicotine is inhaled into the lungs in smoke, enters the bloodstream and travels to the brain in about eight to ten seconds.* The nicotine alters the state of the smoker by becoming a neurotransmitter and a stimulant. *Nicotine mimics the body's most important neurotransmitter, acetycholine (ACH), which controls heart rate and message sending within the brain. The nicotine is used to change physiological states leading to enhanced mental performance and relaxation.* A little nicotine seems to stimulate, while a lot sedates a person.[448]

The report also expressly places cigarettes and smokeless tobacco products in the same category of "nicotine delivery devices" that includes nicotine patches and inhalers, stating that "nicotine delivery devices range from snuff, chewing tobacco, cigars, pipes and conventional cigarettes to unique smoking articles, chewing gum, patches, aerosol sprays and inhalers."[449] The report thus indicates that the views of Philip Morris on the role of nicotine in cigarettes have been remarkably consistent. Twenty years after senior Philip Morris scientist William Dunn called cigarettes "a dispenser for a dose unit of nicotine,"[450] Philip Morris officials continue to regard nicotine as a drug and cigarettes as a "nicotine delivery device." The evidence of Philip Morris' statements and research on

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[447] *Id.* at 1 (emphasis added).

[448] *Id.* (emphasis added).

[449] *Id.* at 2.

[450] Dunn WL (Philip Morris Inc.), *Motives and Incentives in Cigarette Smoking* (1972), at 5. *See* AR (Vol. 12 Ref. 133).

nicotine pharmacology persuasively documents that its cigarettes are intended to affect the structure or function of the body.

b. The Statements and Research of R. J. Reynolds

R.J. Reynolds Tobacco Company (RJR) is the nation's second largest cigarette manufacturer. The information in the administrative record shows that researchers and senior officials at RJR hold views on the pharmacological effects and uses of nicotine in cigarettes that are similar to those of the researchers and senior officials at Philip Morris.

i. The Teague Memoranda. During the comment period, FDA received two documents written by Claude Teague in 1972 and 1973, when he was the assistant director of research at RJR. Teague was subsequently promoted to director of corporate research in 1978.[451] These internal memoranda show that RJR scientists regarded nicotine as a "potent" and "habit-forming" drug; considered cigarettes to be "a vehicle for delivery of nicotine"; and conceived of the tobacco industry itself as "a specialized, highly ritualized and stylized segment of the pharmaceutical industry."

Teague's 1972 memorandum, entitled "Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein," makes four significant points. First, the memorandum describes nicotine as a powerful and habituating drug. According to the memorandum, nicotine is "a potent drug with a variety of physiological effects."[452] It is also "*known to be a habit-forming alkaloid.*"[453] Nicotine's specific effects on the body are described as follows:

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[451] *American Men and Women of Science, 1995-1996,* 19th ed. (New Providence: R.R. Bowker, 1995), 7:62. *See* AR (Vol. 711 Ref. 13).

[452] Teague CE, (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 1. *See* AR (Vol. 531 Ref. 125).

> The habituated user of tobacco products is said to derive "satisfaction" from nicotine. Although much studied, the physiological actions of nicotine are still poorly understood and appear to be many and varied. For example, . . . *at different dose levels, nicotine appears to act as a stimulant, depressant, tranquilizer, psychic energizer, appetite reducer, anti-fatigue agent, or energizer*, to name but a few of the varied and often contradictory effects attributed to it."[454]

Second, the memorandum acknowledges that nicotine is the "primary" reason for smoking. According to the memorandum:

> *[T]he confirmed user of tobacco products is primarily seeking the physiological "satisfaction" derived from nicotine*—and perhaps other active compounds. *His choice of product and pattern of usage are primarily determined by his individual nicotine dosage requirements. . . .*[455]

Third, the Teague memorandum describes cigarettes as drug delivery systems. According to the memorandum, "*a tobacco product is, in essence, a vehicle for delivery of nicotine*, designed to deliver the nicotine in a generally acceptable and attractive form."[456] The memorandum further states:

> If what we have said about the habituated smoker is true, then products designed for him should emphasize nicotine, nicotine delivery efficiency, nicotine satisfaction, and the like. *What we should really make and sell would be the proper dosage form of nicotine with as many other built-in attractions and gratifications as possible*—that is, an efficient nicotine delivery system with satisfactory flavor, mildness, convenience, cost, etc. . . . *Would it not be better, in the long run, to identify in our minds and in the minds of our customers what we are really selling, i.e., nicotine satisfaction?*[457]

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[453] *Id.* (emphasis added).

[454] *Id.* at 1-2 (emphasis added).

[455] *Id.* at 1 (emphasis added).

[456] *Id.*

[457] *Id.* at 5 (emphasis added).